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10/553,704	09/05/2006	Hiromu Habashita	Q90961	4009

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EXAMINER	
JARRELL, NOBLE E	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,704	HABASHITA ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *2,4 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/18/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group II and election of example 1 (page 60) in the reply filed on 4/24/2008 is acknowledged.

Claim Objections

2. Claims 1, 3, 5-15, and 17 are objected to because of the following informalities: they contain non-elected subject matter. In addition, the word "substituent(s)" should be phrased "one or more substiuents". Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3, 5-15, and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In an examination claim 1, the core of the molecule is difficult to determine because of the definitions for variables A, B, G, J, K, and D. What nitrogen-containing ring is ring A? What ring is variable B? What spacer is represented by variable G? What spacer that is also a hydrogen-bond acceptor is represented by variable J? What ring is variable D?

Claims 1, 3, 5-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 3, 5-15 and 17 contain generic definitions for one or more of the variables in each of the claims

According to the MPEP §2163 I. A. "the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." The MPEP states in §2163 II 3 ii) "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406."

According to the MPEP §2163.02 Standard for Determining Compliance with the Written Description Requirement, "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the

written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter". Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))."

This case was filed before Applicants had a clear idea of the structures encompassing the scope of claims 1-2 and 19-22, other than the specific compounds recited in claims 11 and 12. The specification provides broad areas of future research and speculation, inviting undue experimentation in learning how to use Applicants' invention.

Applicants are reminded of what the U.S. Court of Appeals Federal Circuit wrote in University of California v. Eli Lilly and Co. 43 USPQ2d 1398, "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). "It is only a definition of a useful result rather than a definition of what achieves that result." "The description requirement of the patent statute requires a description of an invention, not an indication

of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.")".

5. Claims 1, 3, 5-15, and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a salt or *N*-oxide of a compound of formula (I), does not reasonably provide enablement for a solvate or prodrug of a compound of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants are enabled for the preparation of a salt or *N*-oxide of a compound of formula I but not a solvate or prodrug of a compound of formula I. Applicants do not make any complex compositions comprising a compound of formula I and any of the active agents in claim 17. What is the optimum ratio of the active agents in the complex compositions? Applicants only show formulation examples 1 and 2 (pages 90-91), which show the preparation of simple compositions, that is compositions of a compound of formula I with one or more inactive agents.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compounds embraced by formula (I), compositions comprising them, as well as a method (prevention and/or treatment of diseases induced by a chemokine receptor) of using them.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Vippagunta et al. (*Advanced Drug Delivery Reviews*, **2001**, *48*, 3-26) teach that solvate or hydrate formation is unpredictable within a series of related compounds because each compound responds uniquely to solvate or hydrate formation.

Stella (*Expert Opinion in Therapeutic Patents*, **2004**, *14(3)*, 277-80) teaches that prodrug development requires undue experimentation and there is currently a challenge to develop prodrugs.

(5) The relative skill of those in the art:

One of ordinary skill in the art can replicate the procedure in example 1 of page 60 of the specification.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for preparation of a salt or *N*-oxide of a compound of formula (I).

However, the specification does not provide guidance for preparation of a solvate or prodrug of a compound embraced formula I.

(8) The quantity of experimentation necessary:

Stella (*Expert Opinion in Therapeutic Patents*, **2004**, *14(3)*, 277-80) teaches that prodrug development requires undue experimentation.

Considering the state of the art as discussed by the references above, particularly with regards to claims 1, 3, 5-15, and 17 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

6. Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants are not enabled for the simultaneous treatment and prevention of a chemokine receptor related disease. If a subject already ahs a disease, they can only be treated for a disease. If a subject does not have a disease, a drug can only prevent a disease (such as use of a vaccine). One disease that is induced by chemokine receptors. This disease cannot be prevented by administration of a single drug nor can it can be treated by administration of a single drug.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to prevention and/or treatment of diseases induced by chemokine receptors.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The Merck Medical Manual teaches that HIV is not preventable ("Human Immunodeficiency Virus (HIV) infection", http://merck.com/mmhe/sec17/ch199/ch199a.html, accessed May 19, 2008.). The same reference also teaches that it can only be treated by administration of three types of drugs.

(5) The relative skill of those in the art:

One of ordinary skill in the assays described on pages 88-90.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification does not provide guidance for the simultaneous treatment and prevention of any disease, nor for the treatment or prevention of HIV..

(8) The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, it is shown that compound 1 exhibits an IC_{50} of 4.16 μM *in vitro*. See *Hoffman v. Klaus* 9 USPQ 2d 1657, and *Ex Parte Powers* 220 USPQ 925 regarding types of testing needed to support *in vivo* uses.

Considering the state of the art as discussed by the references above, particularly with regards to claims 14 and 15 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be

burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 3, 5-15, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. What substituents are attached to each of the variables in claim 1? No guidance as to what these variables are is given in the specification. These substituents are mentioned in claims 7-8 as well, which makes these claims indefinite as well. In claim 17, each of the additional agents is unclear. None of the additional agents are adequately defined in the specification to give these terms any concrete meaning.

9. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

10. The attempt to incorporate subject matter into this application by reference to multiple foreign documents for CCR antagonists (pages 51-52) is ineffective because these applicant is not allowed to use foreign documents for explanation of essential subject matter.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1, 3, and 5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al. (WO 02/28880, published 4/11/2002). Suzuki et al. teach compounds 53 and 54 of formula 1-7 (page 52). In compound 53, group R^1-A of formula I is 2,6-dioxo-3-phenyl-piperidine. In compound 54, group R^1-A of formula I is 2,6-dioxo-4,4-dimethyl-piperidine. In each of the compounds, variable B is phenyl, G is CH_2-$CH(CO_2H)$, J is NHC(O), and D is 2,6-di-chloro-phenyl. Since piperidine is a cyclic group is six-membered ring with one nitrogen atom, claims 1, 3, and 5-8 are anticipated.

13. Claims 1, 3, and 5-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Cai et al. (US20070043076, published February 27, 2007, priority to 60/508290, October 6, 2003). Cai et al. teach example 86 (pg 27). In this compound, group R^1-A is 4-methyl-piperidine, B is phenyl, G is CH=C(C(O)NH-3-CF_3-phenyl), J is C(O)NH, and D is 3-CF_3-phenyl. Since piperidine is a cyclic group is six-membered ring with one nitrogen atom, claims 1, 3, and 5-8 are anticipated.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 1, 3, and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Corby et al. (GB 805503, published December 10, 1958). Corby et al. teach example 13, with registry number 103402-24-0. In this compound, variable A is piperidine, B is phenyl, G is $C(O)CH_2$, J is NH(C(O), and D is 2-dimethylamino-4-CO_2H-phenyl. This compound does not teach an alkyl group attached to variable A. However, *in re Lohr* (137 USPQ 548) teaches:

> When new compound so closely related to prior art compound as to be structurally obvious is sought to be patented based on alleged greater effectiveness of new compound for same purpose as old compound, clear and convincing evidence of substantially greater effectiveness is needed.

As a result of *in re Lohr*, claim 13 renders claims 1, 3, and 5-8 obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624